## Spontaneous hair cell regeneration in the neonatal mouse cochlea in vivo.

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**Public Summary:**
Inner ear hair cells are required for hearing, and their loss is the primary cause of sensorineural hearing loss in human. The prevailing notion is that the mammalian cochlea is unable to spontaneously regenerate lost hair cells, thus leading to irreversible hearing loss. However, it is unknown if the immature cochlea may be more regenerative. Using a transgenic approach, we selectively damaged hair cells and found that hair cells can be regenerated to a modest degree in newborn mice. We tracked the origin of regenerated hair cells and found supporting cells to be their source. In non-mammalian species where hair cells are readily regenerated, progenitor cells first divide before transforming into hair cells. In the newborn mice, we found that supporting cells similarly divide and convert into hair cells. However, regenerated hair cells do not survive, the degree of regeneration is limited, and regeneration is limited to a time window immediately after birth. Together, these findings have helped define a population of progenitor cells in the mammalian cochlea capable of spontaneous hair cell regeneration. Future research on these progenitor cells may reveal cues guiding regeneration to restore hearing.

**Scientific Abstract:**
Loss of cochlear hair cells in mammals is currently believed to be permanent, resulting in hearing impairment that affects more than 10% of the population. Here, we developed two genetic strategies to ablate neonatal mouse cochlear hair cells in vivo. Both Pou4f3(DTR/+) and Atoh1-CreER; ROSA26(DTA/+) alleles allowed selective and inducible hair cell ablation. After hair cell loss was induced at birth, we observed spontaneous regeneration of hair cells. Fate-mapping experiments demonstrated that neighboring supporting cells acquired a hair cell fate, which increased in a basal to apical gradient, averaging over 120 regenerated hair cells per cochlea. The normally mitotically quiescent supporting cells proliferated after hair cell ablation. Concurrent fate mapping and labeling with mitotic tracers showed that regenerated hair cells were derived by both mitotic regeneration and direct transdifferentiation. Over time, regenerated hair cells followed a similar pattern of maturation to normal hair cell development, including the expression of prestin, a terminal differentiation marker of outer hair cells, although many new hair cells eventually died. Hair cell regeneration did not occur when ablation was induced at one week of age. Our findings demonstrate that the neonatal mouse cochlea is capable of spontaneous hair cell regeneration after damage in vivo. Thus, future studies on the neonatal cochlea might shed light on the competence of supporting cells to regenerate hair cells and on the factors that promote the survival of newly regenerated hair cells.